Reproductive Factors, Oral Contraceptive Use, and Risk of Colorectal Cancer

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Multiparity and use of oral contraceptives are hypothesized to reduce risk of colorectal cancer. Among 57,529 women, 31–90 years of age, who volunteered for a nationwide breast cancer screening program from 1973 to 1980, we observed 154 pathologically confirmed cases of colon cancer and 49 cases of rectal cancer in up to 10 years of follow-up (388,555 person-years). Parity was not associated with risk of colorectal cancer [age-adjusted rate ratio for ≥4 children *vs* no children = 1.0; 95% confidence interval (CI) = 0.72–1.5], although decreases in proximal colon cancer and increases in distal colon cancer were observed among parous women. The effect of parity did not vary by age at diagnosis. We found no strong or consistent association for age at menarche, age at first birth, or age at natural menopause. In addition, oral contraceptive use, reflecting mainly past use, was unrelated to risk of colorectal cancer (rate ratio = 1.0; 95% CI = 0.75–1.4). These findings do not corroborate the hypothesis that reproductive events or oral contraceptives influence the development of colorectal cancer. (Epidemiology 1997;8:75–79)

Keywords: colorectal cancer, oral contraceptive use, reproductive factors, parity, menopause, menarche, cohort studies.

Results of studies assessing the associations of reproductive factors and oral contraceptive use with colorectal cancer risk are equivocal. Although several studies have reported lower risks for multiparous compared with nulliparous women,[1–8] or compared with women who have had one or two children,[9] others have found no association with parity,[10–18] and two studies[19,20] actually suggested an elevated risk for multiparous women. Overall, there is little support for a protective effect of oral contraceptives,[2,16,19,20–22] with only two studies showing clear reductions in risk.[1,23] Other reproductive factors such as age at menarche, first birth, and menopause have been evaluated, but the findings to date have been inconclusive.[1,2,4–6,12–15,19,24] Some studies have indicated that reproductive or hormonal factors may exert effects mainly on the proximal colon[9] or in older subjects.[6,25] Of the nearly 30 epidemiologic studies that have evaluated the relation of reproductive factors with colon or rectal cancer, only five have been cohort studies.[18–20,26,27]

We investigated the association of various reproductive factors and oral contraceptives and colorectal cancer incidence in a large prospective cohort of U.S. women 31–90 years of age.

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Methods

The Breast Cancer Detection Demonstration Project (BCDDP), sponsored by the American Cancer Society and the National Cancer Institute, was a breast cancer screening program conducted between 1973 and 1980 that included 283,222 women at 29 screening centers in 27 cities throughout the United States. The National Cancer Institute began a cohort study of a subset of the BCDDP participants in 1979. From 1979 to 1986, a baseline interview and up to six annual telephone interviews were administered. A follow-up questionnaire was mailed to subjects between 1987 and 1989.

Exposures and Covariates

At the baseline interview, subjects were asked about reproductive factors and use of birth control pills and female hormones other than birth control pills (excluding creams). Annual telephone interviews and the mailed follow-up questionnaire updated the exposure information. Level of education and measured height and weight were available from forms completed during the screening program. Body mass index (BMI) was defined as weight in kilograms divided by squared height in meters.

Study Population

We excluded women with a diagnosis of breast or colorectal cancer before the start of follow-up from the analytical cohort. There were 57,529 women eligible for study, representing a total of 388,555 person-years of observation; 312,955 person-years were observed among

postmenopausal women. A total of 48,738 (85%) women completed a phase II questionnaire. Reasons for noncompletion of an interview were death (2.5%), illness (<1.0%), refusal (2.5%), end of the study before an interview could be conducted (4.5%), and failure to locate the subject (5%). The majority of the study subjects were white (89%), with small percentages of African-Americans (5%) and Asian-Americans (5%).

Case Identification

Colorectal cancer cases were ascertained on the follow-up questionnaire and by death certificate. Pathology reports were obtained for 86% of women reporting a physician's diagnosis of colorectal cancer after the date of the baseline interview. Pathology reports were not obtained for all potential cases, largely owing to nonresponse by hospitals and physicians. Of the pathology reports retrieved, 96% confirmed a diagnosis of adenocarcinoma of the colon or rectum (*International Classification of Diseases*, 9th revision, codes 153.0–153.9 for colon and 154.0–154.1 for rectal cancer). Self-report of site (colon/rectum) by subjects was less accurate. Deaths due to colorectal cancer were identified from routinely collected death certificates; pathology reports were unavailable for these subjects.

Of 330 cases of colorectal cancer, 241 were identified by the follow-up questionnaire (pathology reports confirmed 203 cases and were not retrieved for 38 cases) and 89 by death certificate. Of the pathologically confirmed cases, 154 had colon cancer, including 75 proximal (cecum to splenic flexure), 63 distal (descending and sigmoid), and 16 unspecified; 49 had rectal cancer. The subsite distribution did not vary by age at diagnosis.

Since the accuracy of self-reporting was high, and death certificate data are generally accurate for colorectal cancer (although less so for colon or rectum, separately),[28] we initially performed the analyses combining the confirmed and unconfirmed cases of colon and rectal cancer. Given difficulties in accurately discriminating between colon and rectal cancers from self-reports or death certificates, however, estimates for the individual sites were based on pathologically confirmed cases.

Statistical Analysis

Follow-up for each woman began with the date of completion of the phase I baseline interview. Person-years were accrued until the earliest of the following dates: first primary diagnosis of colorectal cancer (from the pathology report if available, otherwise, from the questionnaire), death from other causes, last contact, or return of the follow-up questionnaire. We used information on the death certificate, as well as information requested during the annual telephone interviews, to assign dates of cancer diagnosis for cases identified by death certificate.

We treated age, menopausal status, and oral contraceptive use as time dependent in the analyses. We allocated person-years to exposure categories based on exposure status at each year of follow-up.

We defined postmenopausal women as those who had not experienced a menstrual period in the previous 3 months. For analyses evaluating type of menopause or age at menopause, we calculated person-time from the date of baseline interview for women postmenopausal at the beginning of follow-up, or from the date of menopause for premenopausal women who became postmenopausal during follow-up.

We estimated incidence rate ratios and 95% confidence intervals by Poisson regression. We restricted analyses, using pathologically confirmed cases only, to subjects who completed the follow-up questionnaire. Rate ratios for the reproductive factors and oral contraceptive use were unaltered with adjustment for education, weight, height, or BMI; therefore, we present only the age-adjusted estimates in the tables.

TABLE 1. Age-Adjusted Rate Ratio Estimates for Reproductive Factors, Oral Contraceptive Use, and Colorectal Cancer*

	Person-Years	Number of Cases	RR	95% CI
Age (years) at menarche				
≤11	66,820	50	1.0†	
12	98,104	82	1.0	0.71–1.4
13	116,841	92	0.93	0.66–1.3
14	58,081	58	1.1	0.74–1.6
≥15	46,570	45	1.0	0.67–1.5
Parity				
0	53,783	61	1.0†	
1	47,033	41	0.80	0.54–1.2
2	113,709	86	0.82	0.59–1.1
3	90,332	72	0.95	0.68–1.4
≥4	83,579	70	1.0	0.72–1.5
Age (years) at first birth‡				
<20	52,349	39	1.0†	
20–24	156,271	107	0.90	0.62–1.3
25–29	91,429	78	0.95	0.64–1.4
≥30	34,310	45	1.2	0.77–1.8
Type of menopause				
Natural	184,946	204	1.0†	
Bilateral oophorectomy	64,935	50	0.78	0.57–1.1
Unilateral oophorectomy	54,774	47	0.77	0.56–1.1
Age (years) at natural menopause				
<45	19,631	22	1.0†	
45–49	64,639	82	1.4	0.89–2.3
50–54	86,967	88	1.1	0.69–1.8
≥55	13,708	12	0.75	0.37–1.5
OC use				
Never	275,081	273	1.0†	
Ever	113,019	57	1.0	0.75–1.4
Duration (years) of OC use				
<5	75,124	38	1.0	0.70–1.4
≥5	37,895	19	1.1	0.66–1.8

* RR = rate ratio; CI = confidence interval; OC = oral contraceptive. Includes cases self-reported on the follow-up questionnaire and cases identified by death certificate. Excludes 3 cases and 2,136 person-years with missing age at menarche, 117 person-years with missing parity, 411 person-years with missing age at first birth, 5 cases and 3,353 person-years for women whose ovarian status was unknown, 4 cases and 2,787 person-years for women with menopause due to radiation or other, 3 cases and 2,160 person-years for women with missing type of menopause, and 453 person-years with uncertain oral contraceptive use.
† Referent category.
‡ Analyses restricted to parous women.

TABLE 2. Age-Adjusted Rate Ratio Estimates for Reproductive Factors and Colon and Rectal Cancer*

		Colon		Proximal Colon		Distal Colon		Rectum	
	Person-Years	No. of Cases	RR (95% CI)	No. of Cases	RR (95% CI)	No. of Cases	RR (95% CI)	No. of Cases	RR (95% CI)
Age (years) at menarche									
≤11†	62,414	20	1.0	8	1.0	10	1.0	13	1.0
12	91,246	33	1.0 (0.60–1.8)	17	1.3 (0.57–3.1)	14	0.89 (0.39–2.0)	12	0.57 (0.26–1.3)
13	108,592	55	1.4 (0.85–2.4)	25	1.6 (0.71–3.5)	23	1.2 (0.57–2.5)	11	0.43 (0.19–0.97)
14	53,482	26	1.3 (0.71–2.3)	15	1.8 (0.74–4.2)	9	0.90 (0.37–2.2)	6	0.44 (0.17–1.2)
≥15	42,391	19	1.1 (0.60–2.1)	10	1.4 (0.55–3.6)	7	0.85 (0.32–2.3)	7	0.62 (0.25–1.6)
Parity									
0†	48,528	27	1.0	16	1.0	7	1.0	6	1.0
1	42,966	20	0.86 (0.48–1.5)	12	0.89 (0.42–1.9)	6	0.98 (0.33–2.9)	9	1.7 (0.61–4.8)
2	105,896	39	0.79 (0.48–1.3)	17	0.61 (0.31–1.2)	19	1.4 (0.60–3.4)	13	1.2 (0.44–3.1)
3	84,528	38	1.0 (0.63–1.7)	18	0.90 (0.46–1.8)	15	1.5 (0.62–3.8)	10	1.3 (0.45–3.5)
≥4	77,869	30	0.91 (0.54–1.5)	12	0.67 (0.31–1.4)	16	1.8 (0.74–4.5)	11	1.6 (0.57–4.3)
Age (years) at first birth‡									
<20†	47,869	20	1.0	8	1.0	10	1.0	4	1.0
20–24	146,020	48	0.76 (0.45–1.3)	19	0.77 (0.34–1.8)	26	0.82 (0.39–1.7)	20	1.6 (0.55–4.7)
25–29	85,674	41	0.96 (0.56–1.6)	23	1.3 (0.59–3.0)	14	0.65 (0.29–1.5)	10	1.1 (0.36–3.7)
≥30	31,494	18	0.96 (0.50–1.8)	9	1.1 (0.42–2.9)	6	0.67 (0.24–1.9)	9	2.3 (0.70–7.6)
Type of menopause									
Natural†	170,894	91	1.0	46	1.0	35	1.0	30	1.0
Bilateral oophorectomy	60,383	26	0.89 (0.58–1.4)	15	1.0 (0.57–1.8)	9	0.81 (0.39–1.7)	7	0.71 (0.31–1.6)
Unilateral oophorectomy	51,136	24	0.87 (0.55–1.4)	11	0.80 (0.42–1.6)	10	0.93 (0.46–1.9)	8	0.89 (0.41–1.9)
Age (years) at natural menopause									
<50†	77,030	44	1.0	24	1.0	17	1.0	12	1.0
≥50	93,864	47	0.87 (0.57–1.3)	22	0.82 (0.45–1.5)	18	0.96 (0.48–1.9)	18	1.3 (0.61–2.9)

* RR = rate ratio; CI = confidence interval. Includes pathologically confirmed cases only. Excludes 1 case of colon cancer and 1,738 person-years with missing age at menarche, 77 person-years with missing parity, 278 person-years with missing age at first birth, 2 cases of colon cancer and 3,123 person-years for women whose ovarian status was unknown, 2 cases of rectal cancer and 2,508 person-years for women with menopause due to radiation or other, and 3 cases of colon cancer and 1,932 person-years for women with missing type of menopause.
† Referent category.
‡ Analyses restricted to parous women.

Results

The mean duration of follow-up was 6.7 years and ranged from less than 1 year to 10.3 years. The average age of subjects at the start of follow-up was 55.7 years (range = 31–90 years), and 95% of cases occurred among postmenopausal women.

Associations between reproductive factors and colorectal cancer were similar regardless of whether we included cases ascertained by death certificate. We found no relation for age at menarche, parity, age at first birth, or age at natural menopause (Table 1). Women whose menopause was due to bilateral oophorectomy had a slight reduction in risk. In a separate analysis, we found ever-use of menopausal estrogens with or without progestins to be unrelated to overall risk of colorectal cancer, although we noted a slight reduction in risk for current users.[29] Since women with surgical menopause are more likely to have used hormone replacement therapy, we evaluated the relation between type of menopause and colorectal cancer risk by use of postmenopausal hormones; the risks were unchanged (data not shown).

Most likely by chance, pathology reports were retrieved for a higher proportion of cases who used oral contraceptives than for cases who did not. Cases identified by death certificate were less likely to be users of oral contraceptives. Because confirmation of case status and ability to classify by anatomical site were related to the use of oral contraceptives, we present only the results of analyses assessing all colorectal cancers in relation to oral contraceptive use (Table 1). The vast majority of oral contraceptive users had last taken them 5 or more years in the past (95.9%). Use of oral contraceptives was not associated with risk of colorectal cancer.

Risk associated with reproductive factors was also null for colon cancer among pathologically confirmed cases (Table 2). Despite small numbers, risk of distal colon tumors was slightly elevated among parous women but showed little trend with increasing parity ($P_{trend} = 0.61$), whereas risk decreased only slightly with increasing age at first birth ($P_{trend} = 0.74$). In contrast, risk of proximal tumors was slightly reduced among parous women. These results were unaltered with simultaneous assessment of parity and age at first birth as potential mutual confounders (data not shown). Risk of rectal cancer also was elevated for parous women, but there was little trend with increasing parity. There was a reduction in risk of rectal cancer for women who were 12 years of age or older at menarche, but the relation was not monotonic.

Also of interest was the relation of reproductive factors and use of oral contraceptives and colorectal cancer risk by age at diagnosis (Table 3). Although we found no association with age at menarche and colorectal cancer risk for all ages combined (Table 1), age at menarche showed a weak inverse relation with risk among women

TABLE 3. Age-Adjusted Rate Ratio Estimates for Reproductive Factors, Oral Contraceptive Use, and Colorectal Cancer by Age at Diagnosis*

	Age <65 Years at Diagnosis				Age ≥65 Years at Diagnosis			
	Person-Years	No. of Cases	RR	95% CI	Person-Years	No. of Cases	RR	95% CI
Age (years) at menarche								
≤11†	55,120	36	1.0		11,700	14	1.0	
12	76,936	43	0.82	0.53–1.3	21,168	39	1.5	0.82–2.8
13	90,042	42	0.69	0.44–1.1	26,799	50	1.5	0.83–2.7
14	42,371	24	0.81	0.48–1.4	15,710	34	1.7	0.92–3.2
≥15	32,802	18	0.78	0.44–1.4	13,768	27	1.5	0.80–2.9
Parity								
0†	35,580	23	1.0		18,203	38	1.0	
1	31,933	16	0.76	0.40–1.8	15,100	25	0.82	0.50–1.4
2	87,005	36	0.65	0.38–1.1	26,703	50	0.98	0.64–1.5
3	74,030	46	0.99	0.60–1.6	16,301	26	0.85	0.51–1.4
≥4	69,957	44	0.99	0.60–1.6	13,622	26	1.0	0.62–1.7
Age (years) at first birth‡								
<20†	43,255	24	1.0		9,093	15	1.0	
20–24	130,271	67	0.86	0.54–1.4	26,000	40	0.95	0.53–1.7
25–29	68,231	37	0.84	0.50–1.4	23,198	41	1.1	0.61–2.0
≥30	20,988	14	0.98	0.51–1.9	13,321	31	1.4	0.76–2.6
Type of menopause								
Natural†	130,348	96	1.0		54,598	108	1.0	
Bilateral oophorectomy	49,679	27	0.77	0.50–1.2	15,256	23	0.78	0.50–1.2
Unilateral oophorectomy	38,814	22	0.73	0.46–1.2	15,959	25	0.81	0.53–1.3
Age (years) at natural menopause								
<50†	58,773	48	1.0		25,497	56	1.0	
≥50	71,574	48	0.75	0.49–1.1	29,100	52	0.85	0.58–1.2
Ever-use of oral contraceptives								
No†	189,395	116	1.0		85,686	157	1.0	
Yes	108,827	49	0.97	0.69–1.4	4,192	8	1.4	0.65–2.8

* RR = rate ratio; CI = confidence interval. Includes cases self-reported on the follow-up questionnaire and cases identified by death certificate. Excludes 3 cases and 2,136 person-years with missing age at menarche, 117 person-years with missing parity, 411 person-years with missing age at first birth, 5 cases and 3,353 person-years for women whose ovarian status was unknown, 4 cases and 2,787 person-years for women with menopause due to radiation or other, and 3 cases and 2,160 person-years for women with missing type of menopause.
† Referent category.
‡ Analyses restricted to parous women.

under 65 years of age (P_{trend} = 0.28). In contrast, among women age 65 years or older, risk appeared slightly elevated in relation to older ages at menarche (P_{trend} = 0.54). Adjustment for parity slightly attenuated the rate ratio estimates for age at first birth among the younger but not the older women (results not shown). The rate ratio estimates for the remainder of the variables did not differ substantially by age group.

Discussion

The results of this study are consistent with those of all[18–20,26] but one[27] cohort study in providing little evidence for a protective effect of parity on the subsequent risk of colorectal cancer. More support for a protective effect of parity has come from case-control studies, a number of which have noted reduced risks of colorectal,[2–5] colon,[1–3,6–9] and rectal cancer,[3,8,17] associated with high parity. One study[30] found a U-shaped relation between parity and colon cancer, with increased risks among both nulliparous women and women with several children. Several studies, however, have reported no association between parity and risk of colorectal,[11] colon,[10,12–16] or rectal[10,12–15] cancer.

Slattery *et al*[6] have suggested that the discrepant results for parity between case-control and cohort studies may reflect differences in the age distribution of cases, since a higher proportion of younger cases may occur in cohort studies. This hypothesis implies that the effect of parity is more pronounced among older women, but our results and those of another cohort study[18] showed little variation in the association of parity and risk according to age. Two case-control studies, however, indicated a protective effect in older women,[6,7] whereas another indicated an effect in younger women.[9]

We evaluated the colon subsites based on the suggestion of McMichael and Potter[31] that hormone-mediated alterations in bile acids may be more likely to affect the risk of proximal rather than distal tumors. In our study, multiparity was associated with a reduced risk of proximal tumors and an increased risk of distal tumors, but the differences were slight. Whereas one previous study also reported a reduced risk associated with parity for the proximal colon,[27] others have noted an increased risk for the proximal colon,[19] a reduced risk for the distal colon,[8] and a U-shaped relation between parity and risk of distal tumors.[30] In most studies to date, reproductive factors

have not differentially affected tumors of the proximal *vs* distal colon.[12,14,16,18]

One early[1] and one more recent study[23] have reported a reduced risk of colon cancer associated with ever-use of oral contraceptives, but most studies, including ours, have not found important reductions in risk. Three studies reported elevated risks with oral contraceptive use for the proximal colon[22] or rectum,[2,21,22] one observed a reduced risk for the rectum,[32] and two found no association.[16,19]

Similar to the results of our study, most studies have been null for other reproductive factors,[2,5,14,15,17,19] although some case-control studies have reported positive associations between age at first birth and colorectal[4] or colon[1,6,12] cancer, and inverse associations between age at menarche and colon cancer.[13,24]

In summary, our cohort study revealed no relation between a number of reproductive factors and the subsequent risk of colorectal cancer or its subsites. In addition, there was little evidence that the effects of parity and oral contraceptive use are stronger in older women or for the proximal colon, as indicated in some earlier studies. The epidemiologic evidence to date provides little support for the notion that reproductive factors and oral contraceptive use are important determinants of colorectal cancer among women.

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